Conflict of Interest Disclosure

The speaker, Kirsten Ohler, has no real or potential conflicts of interest related to the subject matter in this presentation.

Agenda

Discuss the pharmacological management of the following pediatric disease states:
- Pediatric and neonatal sepsis/meningitis
- Respiratory syncytial virus (RSV)
- Otitis media
- Immunizations
- Pediatric seizure disorders
- Attention deficit hyperactivity disorder (ADHD)

Case 1

Neonate born at 36 week's gestational age develops respiratory distress, hypotension, and mottling at 5 hours of life. Witnessed seizure in the NICU. Mother is GBS positive; three doses of penicillin given before delivery.

Best empiric antibiotic regimen?
- a. Ampicillin + gentamicin
- b. Cefuroxime
- c. Ceftriaxone + vancomycin
- d. Rifampin

Sepsis/Meningitis - Pathogens

| Age         | Organism                      |
|-------------|------|--------------------------------|
| 0 - 1 month | Group B β Streptococcus, E. coli, Listeria, viral, nosocomial |
| 1 - 3 months| Neonatal pathogens, H. influenzae, N. meningitidis, Strep pneumoniae |
| 3 mo - 12 yr| H. influenzae, N. meningitidis, Strep pneumoniae |
| > 12 yr     | N. meningitidis, Strep pneumoniae |

Case 1

Neonate born at 36 week's gestational age develops respiratory distress, hypotension, and mottling at 5 hours of life. Witnessed seizure in the NICU. Mother is GBS positive; three doses of penicillin given before delivery.

Best empiric antibiotic regimen?
- a. Vancomycin
- b. Ampicillin + gentamicin
- c. Ampicillin + ceftriaxone
- d. Cefazidime + gentamicin
Case 2
Culture results reveal gram negative rods in the cerebral spinal fluid.
Which recommendation regarding antibiotic prophylaxis is best?
   a. 5-month old stepsister is at high risk and should receive rifampin
   b. The patient should receive rifampin to eliminate nasal carriage
   c. Antibiotic prophylaxis is not indicated
   d. All close contacts should receive rifampin

Chemoprophylaxis
- Purpose: prevent the spread of *Haemophilus influenzae* and *Neisseria meningitidis*
- High risk groups: household contacts, nursery or child care center contacts, direct contact with patient’s secretions
- Drug of choice: rifampin

Case 3
6-year-old boy presents to the ED with fever, altered mental status & petechiae. No trauma. Tox screen negative. Elevated WBC with a left shift. Cultures are pending.
Best empiric antibiotic regimen?
   a. Ampicillin + gentamicin
   b. Cefuroxime
   c. Ceftriaxone + vancomycin
   d. Rifampin

Sepsis/Meningitis - Pathogens

<table>
<thead>
<tr>
<th>Age</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 month</td>
<td>Group B</td>
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<td><em>H. influenzae, N. meningitidis, Strep pneumoniae</em></td>
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<tr>
<td>&gt; 12 yr</td>
<td><em>N. meningitidis, Strep pneumoniae</em></td>
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Case 3
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Best empiric antibiotic regimen?
   a. Ampicillin + gentamicin
   b. Cefuroxime
   c. Ceftriaxone + vancomycin
   d. Rifampin
Case 4

You are screening babies during RSV season for risk factors associated with the development of severe RSV infection.

Which of the following is the best recommendation to make regarding the use of palivizumab for RSV prophylaxis?

Palivizumab should NOT be prescribed for:

- A 34 weeks’ gestation baby with a cyanotic congenital heart defect
- A 21-day-old, 31 weeks’ gestation baby, only child, non-smoking parents, will not attend day care
- A 5-month-old, 29 weeks’ gestation infant, history of CLD, no O₂ or meds
- An 18-month-old, 26 weeks’ gestation infant history of CLD, no O₂ or meds in past 8 mo

Respiratory Syncytial Virus

- Risk Factors
  - premature birth
  - chronic lung disease (CLD)
  - cyanotic or complicated congenital heart disease
  - immunodeficiency
  - airway abnormalities
  - other: low socioeconomic status, passive smoking, day care, siblings

Respiratory Syncytial Virus

- AAP recommendations for prophylaxis
  - infants born < 32 weeks who are < 6 mo at the beginning of RSV season
  - infants with CLD who are ≤ 2 yo and require medical management of CLD w/in last 6 months
  - infants between 32 - 34 weeks, 6 days gestation who are ≤ 3 mo at the beginning of RSV season with risk factors may benefit
  - infants ≤ 24 months of age with hemodynamically significant congenital heart disease

Case 5

18-month-old with history of premature birth and CLD is admitted to the PICU with respiratory distress requiring intubation, fever, and a 3-day history of cold-like symptoms. A nasal swab is positive for respiratory syncytial virus.
Case 5
Which is the best intervention?
- a. Palivizumab
- b. Corticosteroids
- c. Cefuroxime
- d. Intravenous fluids and supportive care

Case 6
A 5-month-old infant, born at term, healthy is treated for her first case of otitis media with amoxicillin 45 mg/kg/day for 7 days. Follow-up exam shows fullness of middle ear, cloudy TM. Afebrile and eating well.
Best treatment recommendation?
- a. No antibiotics are warranted at this time
- b. High-dose (90 mg/kg/day) amoxicillin x 7 days
- c. Decongestant & antihistamine daily
- d. Azithromycin

Otitis Media
- Common pathogens
  - viral
  - Streptococcus pneumoniae
  - nontypeable Haemophilus influenzae
  - Moraxella catarrhalis

Case 7
4-year-old boy diagnosed with 4th case of otitis media in 12 months. No evidence of hearing loss or delayed language skills.
Which of the following is the best intervention?
- a. Long-term antibiotic prophylaxis
- b. Tympanostomy tubes
- c. High-dose amoxicillin and ensuring he is up-to-date on pneumococcal and influenza vaccines
- d. No antibiotic therapy is warranted
Case 8
1-year-old boy with history of Kawasaki disease treated 4 months ago with IVIG. At well-child check-up, due for MMR and varicella. Mother has several concerns regarding immunizations.

Best reason to defer administration of vaccines?
- a. Association between MMR & autism
- b. Allergic reaction to MMR if patient has egg allergy
- c. Many concurrent vaccines can overload immune system
- d. Decreased vaccine efficacy because of previous IVIG administration

Case 9
For which of the following patients would it be best to recommend deferring immunizations?
- a. 12-month-old boy who recently completed a cycle chemotherapy for ALL
- b. 6-month-old girl on amoxicillin for otitis media
- c. 12-month-old, HIV-positive boy with CD4 >1000
- d. 12-year-old girl completing a prednisone “burst” (1 mg/kg/day) for asthma exacerbation

Immunizations

- Barriers to routine immunization
  - contraindications
    - anaphylactic reaction to the vaccine
    - acute moderate – severe febrile illness
    - immunodeficiency, pregnancy, recent IVIG
    - encephalopathy within 7 days of previous DTaP
  - misconceptions regarding contraindications
    - mild acute illness, current antibiotics, etc.

Immunizations

- Special populations
  - Preterm infants
    - immunize based on chronologic age
  - Immunocompromised children
    - no live vaccines
  - Patients receiving corticosteroids
    - recommendations depend on steroid dose / duration
  - Patients who recently received IVIG
    - affects live vaccines (ex. MMR, varicella)
    - recommendations depend on indication / dose of IVIG
  - HIV-infected patients
    - recommendations depend on degree of immunocompromise

Immunizations

- Recent changes to the routine schedule
  - 7-valent conjugated pneumococcal vaccine (PCV-7) replaced with 13-valent product (PCV-13)
  - Human papilloma virus (HPV) vaccine indicated for males 9-26 years for prevention of genital warts
Immunizations

- Special populations
  - Preterm infants
    - Immunize based on chronologic age
  - Immunocompromised children
    - No live vaccines
  - Patients receiving corticosteroids
    - Recommendations depend on steroid dose / duration
  - Patients who recently received IVIG
    - Affects live vaccines (ex. MMR, varicella)
  - HIV-infected patients
    - Recommendations depend on degree of immunocompromise

Case 9
For which of the following patients would it be best to recommend deferring immunizations?

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- c. 12-month-old, HIV-positive boy with CD4 >1000
- d. 12-year-old girl completing a prednisone "burst" (1 mg/kg/day) for asthma exacerbation

Case 10
14-year-old moderately obese girl complains of erythematous pruritic rash. She was started on oxcarbazepine three weeks ago for partial seizures. Sexually active + contraception.

Which of the following is the best intervention?

- a. Change to carbamazepine
- b. Change to levetiracetam
- c. Change to valproic acid
- d. No change in therapy is necessary

Pediatric Seizures

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Drugs of Choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>VPA, CBZ, PHT</td>
<td>PB, Gabapentin, Lamotrigine, [ ]</td>
</tr>
<tr>
<td>Generalized</td>
<td>VPA, CBZ, PHT</td>
<td>Lamotrigine, Topiramate, Zonisamide, Levetiracetam</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>VPA</td>
<td>Topiramate, Zonisamide, Levetiracetam</td>
</tr>
<tr>
<td>Absence</td>
<td>Ethosuximide, VPA</td>
<td>Lamotrigine, Zonisamide, Levetiracetam</td>
</tr>
<tr>
<td>Lennox-Gastaut</td>
<td>VPA, Topiramate, Lamotrigine</td>
<td>Felbamate, Zonisamide</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>ACTH</td>
<td>Lamotrigine, Topiramate, [ ] VPA, Zonisamide</td>
</tr>
</tbody>
</table>
### Pediatric Seizures

<table>
<thead>
<tr>
<th>Rash</th>
<th>Weight gain</th>
<th>Weight loss</th>
<th>Cognitive/CNS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Valproic acid</td>
<td>Topiramate</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Gabapentin</td>
<td>Zonisamide</td>
<td>Topiramate</td>
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<tr>
<td>Lamotrigine</td>
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<td>Valproic acid</td>
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<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Menstrual irregularities:**
- Valproic acid
- Phenytoin
- Phenytoin
- Zonisamide

### Case 10

14-year-old moderately obese girl complains of erythematous pruritic rash. She was started on oxcarbazepine three weeks ago for partial seizures. Sexually active + contraception.

Which of the following is the best intervention?
- a. Change to carbamazepine
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### Case 11

9-year-old boy is newly diagnosed with ADHD symptoms at home and school.

Best recommendation for initial drug regimen?
- a. Methylphenidate OROS (Concerta®) once daily
- b. Methylphenidate IR (Ritalin®) twice daily given four hours apart
- c. Guanfacine at bedtime
- d. D-methylphenidate (Focalin®) twice daily given four hours apart

### Drug Therapy for ADHD

- **Stimulants**
  - Methylphenidate-containing products
  - Amphetamine-containing products

- **Non-stimulants**

### Drug Therapy for ADHD

- **Methylphenidate-containing products**
  - duration of effect
    - short = Ritalin and Focalin
    - intermediate = Metadate ER and Ritalin SR
    - long = Concerta, Metadate CD, Ritalin LA
  - side effects
    - insomnia, loss of appetite, headache, may exacerbate tics

- **Amphetamine-containing products**
  - duration of effect
    - Adderall vs. Adderall XR
  - side effects
    - insomnia, loss of appetite, nervousness, exacerbation of hypertension and tics
    - potential association with sudden cardiac death
Drug Therapy for ADHD

- Non-stimulant medications
  - Atomoxetine (Strattera)
    - potential association with severe liver injury
    - does not exacerbate tics
  - Clonidine
    - more effective for hyperactivity than inattention
    - lessens the severity of tics
    - sedation
  - Guanfacine
    - ↓ sedation and ↑ duration than clonidine

Case 11

9-year-old boy is newly diagnosed with ADHD symptoms at home and school.

Best recommendation for initial drug regimen?

- a. Methylphenidate OROS (Concerta®) once daily
- b. Methylphenidate IR (Ritalin®) twice daily given four hours apart
- c. Guanfacine at bedtime
- d. D-methylphenidate (Focalin®) twice daily given four hours apart

Case 12

The patient is started on methylphenidate OROS (Concerta®); symptoms well-controlled, but complaining of insomnia.

Best modification to treatment regimen?

- a. Administer Concerta later in day
- b. Change to methylphenidate modified release (Metadate CD) once a day.
- c. Change to methylphenidate patch
- d. Change to atomoxetine at bedtime

Questions

Conflict of Interest Disclosure

- The speaker, Jennifer Dugan, has no real or potential conflicts of interest related to the subject matter in this presentation.
Patient Case 1

NH is an 85 yo woman in a nursing facility.
- Type 2 DM, HTN, moderate dementia due to CVA, s/p hip fracture.
- Glyburide 10 mg/d, lisinopril 10 mg/d, metformin 500 mg BID, donepezil 10 mg/d, aspirin 81 mg/d, MVI, zolpidem 5 mg QHS PRN, Meclizine 12.5 mg TID PRN, bowel regimen

Patient Case # 1cont.
Which of the following functional assessments is most important?
A. IADLS
B. Assessment for depression
C. Assessment for gait and balance
D. Assessment for pressure sores

Physiologic Changes in the Elderly Pearls
- Absorption from transdermal patches may be reduced if insufficient subcutaneous fat
- Distribution may be increased for highly protein-bound meds
- Metabolism impacts benzodiazepine choices
- Elimination is not just about Serum Creatinine

Patient Case # 2
Labs for NH include fasting glucose 90 mg/dL, sodium 138 mEq/L, potassium 4.5 mEq/L, chloride 102 mEq/L, CO2 25 mEq/L, blood urea nitrogen 30 mg/dL, SCr 1.8 mg/dL, and TSH 4.0 mU/L. Which one of the following pharmacokinetic parameters is most likely to be changed in N.H.?
A. Oral absorption
B. Distribution
C. Metabolism
D. Renal excretion

N.H. meds
- Glyburide 10 mg/day
- Lisinopril 10 mg/day
- Metformin 500 mg BID
- Donepezil 10 mg/day
- Aspirin 81 mg/day
- MVI

Patient Case # 3
Based on your assessment of age- and disease-related changes in N.H., which one of the following areas of pharmacotherapy is best to address first?
A. Diabetes management
B. Alzheimer disease treatment
C. Hypertension treatment
D. Stroke prevention
Patient Case # 4
To maintain and improve function in N.H., which one of the following interventions is best to implement?

A. Add a calcium and vitamin D supplement
B. Add simvastatin 10 mg/day
C. Add warfarin
D. Assess for incontinence and treat with anticholinergic agents

Handout Page 1-40; Answer Page 1-64

Common Drug Related Problems in Elderly
- Overuse
- Underuse
  - ACE inhibitors in CHF, anticoagulation in A fib, drug therapy post MI, untreated depression
- Medication Adherence
  - Intentional nonadherence related to perceived overmedication, ADRs, cost
- Use of inappropriate medications
- Adverse drug events

Potentially Inappropriate Medications
- Common offenders
  - Diphenhydramine
  - Long Acting Benzos (Diazepam, Chlordiazepoxide)
  - Skeletal Muscle Relaxants
  - Amitriptyline, Doxepin, Imipramine
  - GI antispasmodics and other anticholinergics
  - Indomethacin, Piroxicam
  - Promethazine
  - Butalbital compounds
  - Propoxyphene

Change in MMSE scores over time for pts receiving AChEIs

Treating Adverse Effects with New Med

- Watch for prescribing cascade:
  - Metoclopramide → Parkinsonian sxs → Levodopa
  - Donepezil → Incontinence → Oxybutynin
  - Diphenhydramine → Urinary Retention → Terazosin
  - Dihydropyridine CCB → Edema → Furosemide

Patient Case # 6
An 87-year-old man with Alzheimer disease is on rivastigmine 6 mg 2 times/day. His family notes improvement in his functional ability but reports that he is experiencing nausea and vomiting that seem related to rivastigmine.

Which one of the following is the best course to take?
A. Advise the patient to take his drug with an antacid.
B. Add prochlorperazine 25 mg by rectal suppository with each rivastigmine dose.
C. Discontinue rivastigmine and initiate memantine 5 mg twice daily.
D. Change rivastigmine to the daily patch that delivers 9.5 mg/day.

Symptoms of Dementia

- Functional disability
- Cognitive impairments
- Behavioral and psychological symptoms

Prevalence of Types of Dementia

Delirium

- Disturbance of consciousness and difficulty with attention
- Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance)
- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
- Evidence from the history, physical examination, or laboratory findings is present that indicates the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Key Symptoms</th>
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<tbody>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations, Parkinsonian sx, fluctuating alertness</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>Acute onset, stepwise deterioration, focal neurologic signs</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>Slow onset, progressive decline</td>
</tr>
</tbody>
</table>
Therapy for Dementia

- Acetylcholinesterase Inhibitors
  - Donepezil
  - Galantamine
  - Rivastigmine
- Memantine
- Efficacy and Safety Pearls

GI effects from AChEIs

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine po</th>
<th>Rivastigmine patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>19%</td>
<td>24%</td>
<td>47%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>13%</td>
<td>31%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>12%</td>
<td>19%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Evaluating Efficacy

- Evaluate patient in 3-6 months to determine need for continued treatment
- Utilize caregiver reports, MMSE/SLUMS, and/or ADLs
- No change or mild improvement at 6 months → continue treatment
- Continued decline on therapy → consider discontinuation or changing medication
- 4 points/year is average decline without treatment

Patient Case # 7
RA is 75 yo woman with Alzheimer disease on donepezil 10 mg/day for 3 years. MMSE 21/30 → 17/30. RA is at home with husband - can’t do IADLs but can do ADLs with cueing.

Which one of the following is the best course of action?

A. Change her treatment from donepezil to rivastigmine.
B. Stop donepezil.
C. Add memantine 5 mg/day.
D. Add vitamin E 400 units 2 times/day.

Evaluating Efficacy

- Evaluate patient in 3-6 months to determine need for continued treatment
- Utilize caregiver reports, MMSE/SLUMS, and/or ADLs
- No change or mild improvement at 6 months → continue treatment
- Continued decline on therapy → consider discontinuation or changing medication
- 4 points/year is average decline without treatment

Patient Case # 8
87- yo woman in dementia unit. PMH: AD, PD, OA, requiring total assistance with bathing and dressing and help with feeding. Meds: donepezil 10 mg/day, memantine 10 mg 2 times/day, carbidopa/levodopa 25/100 mg 4 times/day, oxybutynin extended release 5 mg/day, and MVI. MMSE score is 5/30, and GDS is 4/15. Patient crying out “Help me, help me.” Which one of the following additional assessment tools is most necessary in assessing this patient?

A. Brief Psychiatric Rating Scale
B. Functional Assessment Staging
C. An evaluation of incontinence
D. Framingham Risk Assessment

Handout Page 1-48; Answer Page 1-64

Patient Case # 9
87- yo woman in dementia unit. PMH: AD, PD, OA, requiring total assistance with bathing and dressing and help with feeding. Meds: donepezil 10 mg/day, memantine 10 mg 2 times/day, carbidopa/levodopa 25/100 mg 4 times/day, oxybutynin extended release 5 mg/day, and MVI. MMSE score is 5/30, and GDS is 4/15. Patient crying out “Help me, help me.” Which one of the following changes would be best to reduce inappropriate medications?

A. Change carbidopa/levodopa to a continuous release formulation.
B. Discontinue oxybutynin
C. Discontinue memantine
D. Reduce dose of donepezil

Handout Page 1-48; Answer Page 1-65
Patient Case #10
This same patient (MMSE 5/30, GDS 4/15) is medically assessed, and reversible causes of her hyper-vocalization are ruled out. Which one of the following represents the best approach to treating her behavioral symptoms?

A. Implement a behavioral approach
B. Add valproic acid
C. Add quetiapine
D. Add citalopram

Handout Page 1-48; Answer Page 1-65

General Approach to Behaviors in Dementia

- Define target agitated behavior
- Consider contributing causes
- Address ALL causes
- Non-pharmacologic measures
- Pharmacologic interventions

Lyketsos et al, Am J Geriatr Psychiatry July 2006;14:7

Examples of Non-pharmacologic Interventions

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Causes</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Discomfort, pain</td>
<td>Assess/manage pain, constipation, infection</td>
</tr>
<tr>
<td></td>
<td>Physical illness (UTI)</td>
<td>Evaluate medically, treat</td>
</tr>
<tr>
<td></td>
<td>Overstimulation-noise, TV, people, etc</td>
<td>Reduce noise, stress, limit TV, crowding</td>
</tr>
<tr>
<td>Paranoia</td>
<td>Forgot where placed object</td>
<td>Offer to help find, have more than one of same object</td>
</tr>
<tr>
<td></td>
<td>Misinterpreting actions or words</td>
<td>Do not argue or try to reason, do not take personally, distract</td>
</tr>
<tr>
<td></td>
<td>Change in environment</td>
<td>Familiarize, reassure, set routine</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Depression</td>
<td>Treat with antidepressant</td>
</tr>
<tr>
<td></td>
<td>Less need for sleep</td>
<td>Later bedtime, more exercise</td>
</tr>
</tbody>
</table>


When should we consider pharmacologic treatment of BPSD?

- Behavior is dangerous, distressing, damaging to social relationships and persistent

AND

- Has not responded to comprehensive non-pharmacologic treatment plan, including removal of possibly offending drugs

OR

- Requires emergency treatment to allow proper investigation of underlying problems

Pharmacologic Treatment

- Cochrane review suggests best evidence is with risperidone and olanzapine for psychosis and aggression
- Start at low doses
- Use quetiapine if patient has comorbid Parkinson’s disease or Lewy Body Dementia
- Use for shortest duration possible
- Adverse effects include increased mortality; recent cohort study* suggests worse with haloperidol, less with quetiapine

*BMJ 2012;344:e977

Patient Case #11
A 75-year-old woman reports urinary urgency, frequency, and loss of urine when she cannot make it to the bathroom in time. She wears a pad at night that she changes 2 or 3 times. PMH: Alzheimer disease (MMSE 23), osteoarthritis, and hypothyroidism.

UA negative, exam WNL, PVR normal.

Which of the following interventions would be best?

A. Bethanechol
B. Pelvic floor muscle exercises plus estrogen vaginal cream
C. Darifenacin
D. Oxybutynin

Handout Page 1-53; Answer Page 1-65
Normal Urination

- STORAGE - under sympathetic control
  → inhibition of detrusor contraction
  → increase sphincter contraction
- URINATION - under parasympathetic control
  → induces detrusor contraction
  → induces sphincter relaxation
- Urethral sphincter:
  - proximal smooth muscle contracts via sympathetic stimulation
  - distal urethral striated muscle via cholinergic stimulation

Types of Urinary Incontinence

- Functional
- Urge (Bladder overactivity)
- Stress (Urethral underactivity)
- Overflow (Urethral overactivity/Bladder underactivity)
- Mixed

Nonpharmacologic Interventions

- Pelvic floor exercises (Kegel exercises)
- Bladder training
- Biofeedback
- Scheduled/Timed Voiding
- Avoid aspartame, spicy/citrus foods, caffeine, carbonated beverages
- Pessaries/bladder neck support prostheses

Treatment of UI

- Functional
  - Assist with functional disabilities
  - Scheduled bathroom visits
  - Bedside commode
  - Stop precipitating drugs
- Urge
  - Nonpharmacologic interventions
  - Anticholinergics (generally equivalent efficacy)

Anticholinergic Adverse Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dry mouth %</th>
<th>Constipation %</th>
<th>Dizziness %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>88</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Oxy ER/XL</td>
<td>68</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Oxy TDS</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Oxy gel</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>50, 39</td>
<td>10, 10</td>
<td>4, 3</td>
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<td>Fesoterodine</td>
<td>99</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Trospium</td>
<td>33</td>
<td>11</td>
<td>?</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>34</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>59</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment of overactive bladder in women. AHRQ Publication No. 09-E017. 8/09
**Treatment of UI**

- **Stress**
  - Kegel exercises, pessaries, surgery
  - Consider stopping precipitating medications
    - Alpha-1 blockers, methyldopa, ACE inhibitors
  - Vaginal estrogens?
  - Alpha agonists?
  - Duloxetine?

- **Overflow**
  - Consider stopping precipitating medications
    - Alpha agonists, beta-blockers, TCAs, anticholinergics, CCBs, diuretics, muscle relaxants
  - Treatment of BPH
  - Cholinergic stimulation?

**Patient Case #12**

A.W. is an 85-year-old man who presents to his physician with LUTS. A digital rectal examination confirms the diagnosis of BPH. Ultrasound shows prostate volume is 31 g. A.W.’s score on the AUASI is 15. His BP is 118/70 sitting, 102/62 standing.

**Which of the following interventions would be best?**

A. Terazosin  
B. Finasteride  
C. Tamsulosin  
D. Finasteride plus tamsulosin

Handout Page 1-55; Answer Page 1-65

**BPH**

- **Alpha Blockers**
- **Alpha Reductase Inhibitors**
- **Combination Therapy**
  - May be needed in men with LUTS, a larger prostate size (>40g), and an elevated PSA

**Patient Case #13**

W.F. is an 85-year-old man with pain from hip OA. He also has hypertension, coronary artery disease, and BPH. For his OA, W.F. has been taking acetaminophen 650 mg 3 times/day. W.F. reports that acetaminophen helps, but he still experiences pain that limits his ability to walk.

**Which of the following interventions would be best?**

A. Change the analgesic to celecoxib  
B. Add hydrocodone  
C. Change the analgesic to ibuprofen  
D. Add glucosamine

Handout Page 1-58; Answer Page 1-65

**Osteoarthritis**

- **Nonpharmacologic Treatment**
- **Acetaminophen dosing**
- **NSAIDs vs Opioids**
- **Preventing adverse effects**
- **Glucosamine**

**Patient Case #14**

F.A. is a 55 yo woman with RA. Diagnosed 1 year ago, she began therapy with methotrexate, and she is presently receiving 15 mg every week, folic acid 2 mg/day, ibuprofen 800 mg 3 times/day, and omeprazole 20 mg/day. Today F.A. reports a recurrence of her symptoms. Radiographic evaluation of her hand joints shows progression of joint space narrowing and bone erosion.

**Which of the following interventions would be best?**

A. Administer etanercept  
B. Switch to hydroxychloroquine  
C. Add prednisone bridge therapy  
D. Change to leflunomide

Handout Page 1-59; Answer Page 1-65
Rheumatoid Arthritis

- DMARDs first line
  - MTX
  - Hydroxychloroquine
  - Sulfasalazine
  - Leflunomide
- Biologic Treatments
- NSAIDs and Corticosteroids
  - Short term
  - No effect on disease progression

Questions

- ??????

Learning Objectives

1. Review and apply national guideline treatment strategies for the following gastrointestinal (GI) disorders: gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), ulcerative colitis, Crohn’s disease, viral hepatitis, chronic liver disease, upper GI bleeding, constipation, diarrhea, irritable bowel syndrome (IBS), nausea, vomiting, pancreatitis, prevention of stress-related mucosal disease (SRMD).

2. Recommend appropriate pharmacologic and nonpharmacologic interventions for the treatment of GERD.

3. Differentiate between clinical signs, symptoms, risk factors, and treatment of both *Helicobacter pylori* and nonsteroidal anti-inflammatory drug (NSAID)-associated PUD.

4. Discuss the role of pharmacologic intervention in the treatment of nonvariceal upper GI bleeding.

5. Review the clinical differences in signs, symptoms, and treatment of Crohn’s disease and ulcerative colitis.

6. Identify the common manifestations of chronic liver disease and their treatment.

7. Review the treatment of both acute and chronic viral hepatitis.
Learning Objectives
8. Recognize pertinent information for educating patients and prescribers regarding the appropriate use of pharmacologic agents for various GI disorders.

9. Recommend appropriate pharmacologic and nonpharmacologic interventions for diarrhea and constipation.

10. Review recommendations for the treatment and prevention of nausea and vomiting.

Learning Objectives
11. Discuss the clinical and treatment differences between acute and chronic pancreatitis.

12. Discuss the role of pharmacologic intervention in the treatment of IBS.

13. Understand commonly encountered statistical tests and concepts using GI disorders as examples.

Patient Case # 1
- HPI: 55 year old man with 8 month history of GERD symptoms 4-5 days/week. Prescriber wishes to initiate esomeprazole 20 mg/day.
- PMH: GERD, MI, HF, Hypothyroidism
- MEDS: Ranitidine + Calcium Carbonate, Metoprolol, Furosemide, Lisinopril, Aspirin

Which one of the following baseline tests is best to perform in this patient today before initiating his esomeprazole therapy?
A. Peripheral bone mineral density screening.
B. Serum magnesium.
C. Serum potassium.
D. Chest radiograph.

Treatment of GERD
- Nonpharmacologic/Lifestyle modifications
  - Targeted
  - Antacids
  - Acid suppression (as needed or scheduled)
    - Proton Pump Inhibitors
    - Histamine-2 Receptor Antagonists
  - Promotility Agents
  - Proper patient education
  - Surgical intervention

PPI Safety Concerns

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Prevention and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Fracture (Hip, wrist, spine)</td>
<td>Re-evaluate need, limit dose and duration, ensuring adequate Calcium and Vitamin D, BMD screening if at risk for low bone mass, weight-bearing exercise.</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Re-evaluate need, limit dose and duration, baseline testing (diuretics, digoxin), supplementation.</td>
</tr>
<tr>
<td>Clostridium difficile associated diarrhea</td>
<td>Re-evaluate need, limit dose and duration, evaluate for C. difficile if patient receiving PPI has diarrhea that is not improving, have patients report diarrhea, report cases to MedWatch.</td>
</tr>
</tbody>
</table>

Handout Page 1-81; Answer Page 1-137
Patient Case # 1
Which one of the following baseline tests is best to perform in this patient today before initiating his esomeprazole therapy?

A. Peripheral bone mineral density screening.
B. Serum magnesium.
C. Serum potassium.
D. Chest radiograph.

Handout Page 1-81; Answer Page 1-137

Patient Case # 2
HPI: 68 year old female with heme positive stools anemia and abdominal pain. Use of OTC ketoprofen for 2 months.

PMH: Type 2 DM, Peripheral neuropathy, Hypertension

Meds: metformin, aspirin, gabapentin, lisinopril

Diagnostics: endoscopy reveals 1 cm gastric ulcer with an intact clot, H. pylori negative via CLO Test

Handout Page 1-87; Answer Page 1-137

Peptic Ulcer Disease (PUD)

Classification
- Duodenal ulcer
- Gastric ulcer

Etiologies
- Helicobacter pylori (carcinogen)
- NSAIDs

Symptoms
- Epigastric pain, nausea, anorexia, belching
- May be temporally related to food intake

NSAID Associated PUD

NSAIDs have topical and systemic adverse GI effects
- COX-2 vs. COX-1 effects

Risk Factors
- Age >60, History of PUD +/- complications
- Corticosteroids, anticoagulants, low dose aspirin, aspirin, ↑ NSAID dose

Contributing factors
- H. pylori, Smoking, CVD, RA, SSRIs

Management of NSAID-Associated PUD

- Remove and reevaluate need for NSAID and/or aspirin
  - Test for H. pylori and treat if positive

- Acid suppression
  - PPI for 8-12 weeks

- Misoprostol
  - COX-2 Inhibitors
    - Cardiovascular risks
    - Use with aspirin
Patient Case # 2

Which one of the following treatments is best for this patient’s ulcer?

- A. Ranitidine 150 mg 2 times/day for 4 weeks
- B. Lansoprazole 30 mg 2 times/day plus amoxicillin 1000 mg 2 times/day plus clarithromycin 500 mg 2 times/day for 10 days
- C. Lansoprazole 30 mg/day for 8 weeks
- D. Misoprostol 200 mcg 4 times/day for 8 weeks.

Handout Page 1-87; Answer Page 1-137

Patient Case # 3

HPI: 42 year old male with sharp epigastric pain for 6 weeks. Pain is worse with eating and is present approximately 5 days per week. Some relief with OTC antacids.

- MEDS: antacids as needed
- Allergies: Penicillin (severe rash)
- UBT for *H. pylori* is positive

Handout Page 1-87; Answer Page 1-137

Patient Case #3

Which one of the following treatments for *H. pylori* is best?

- A. Amoxicillin, clarithromycin, omeprazole for 10 days
- B. Cephalexin, clarithromycin, omeprazole for 10 days
- C. Bismuth, tetracycline, metronidazole, omeprazole for 14 days
- D. Levofloxacin, metronidazole, omeprazole for 10 days

Handout Page 1-87; Answer Page 1-137

Diagnosis of *H. pylori*

- Invasive testing (endoscopic)
  - Histology
  - Rapid urease (affected by antisecretory agents)
  - Culture

- Non-invasive testing
  - Serologic (IgG)
  - Urea breath test (affected by antisecretory agents)
  - Fecal antigen (affected by antisecretory agents)

Treatment of *H. pylori*

- Triple therapy
  - PPI + amoxicillin or metronidazole + clarithromycin
  - 10-14 days of treatment (14 preferred)
  - Efficacy affected by previous macrolide exposure

- Quadruple Therapy
  - PPI + Bismuth + Metronidazole + Tetracycline
  - 1st line, PCN allergy, previous macrolide exposure, failure of triple therapy
  - 10-14 days of treatment

Patient Case #3

Which one of the following treatments for *H. pylori* is best?

- Amoxicillin, clarithromycin, omeprazole for 10 days
- Cephalexin, clarithromycin, omeprazole for 10 days
- Bismuth, tetracycline, metronidazole, omeprazole for 14 days
- Levofloxacin, metronidazole, omeprazole for 10 days

Handout Page 1-87; Answer Page 1-137
**Patient Case #4**

- **HPI:** 35 year old male with ulcerative colitis (majority of colon). Experiences 5-6 bloody bowel movements per day when prednisone is reduced to less than 40mg/day.
- **MEDS:** Balsalazide 6.75 g/day x 2 years, prednisone 40 mg/day x 1 year

Handout Page 1-100; Answer Page 1-137

**What would be an appropriate modification of his drug regimen at this time?**

A. Change balsalazide to sulfasalazine 6g/day  
B. Initiate therapy with methotrexate IM weekly  
C. Initiate infliximab and taper prednisone  
D. Add mesalamine suppository daily

Handout Page 1-100; Answer Page 1-137

**Clinical Findings**

<table>
<thead>
<tr>
<th>Bowel Involvement</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum/Colon</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Perianal Involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Depth</td>
<td>Superficial</td>
<td>Submucosa/deeper</td>
</tr>
<tr>
<td>Pattern of inflammation</td>
<td>Continuous</td>
<td>Patchy</td>
</tr>
<tr>
<td>Histology</td>
<td>Crypt abscesses</td>
<td>Granulomas</td>
</tr>
<tr>
<td>Fistula, perforation, or Strictures</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Pseudopolyps</td>
<td>Common</td>
<td>Fairly Common</td>
</tr>
</tbody>
</table>

**Drug Treatment Options**

- **5-Aminosalicylates**  
  - Sulfasalazine  
  - Mesalamine  
  - Olsalazine  
  - Balsalazide

- **Immunomodulators**  
  - Azathioprine  
  - 6-Mercaptopurine  
  - Methotrexate  
  - Cyclosporine  
  - Tacrolimus

- **Biologics**  
  - Infliximab  
  - Adalimumab  
  - Certolizumab  
  - Natalizumab

**Approach to the Treatment of IBD**

1. Identify disease: UC vs. CD
2. Severity: Active (mild to fulminant) or remission  
3. Determine extent and location of disease  
4. Pick drug(s) based on  
   - Onset of action  
   - Formulation (Oral, Topical, Parenteral)  
   - Effectiveness  
   - Potential adverse effects or contraindications

**IBD Treatment Guidelines**

<table>
<thead>
<tr>
<th>Severity</th>
<th>UC</th>
<th>Crohn’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Moderate</td>
<td>Aminosalicylate</td>
<td>Aminosalicylate or Budesonide (oral)</td>
</tr>
<tr>
<td>Moderate to Severe</td>
<td>Infliximab OR Azathioprine/6-MP +/- Corticosteroid (short-term)</td>
<td>TNF-α inhibitor OR Azathioprine/6-MP OR Methotrexate +/- Corticosteroid (short-term) OR Natalizumab (last line)</td>
</tr>
</tbody>
</table>
Key Safety Concerns in IBD

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-alpha antagonists</td>
<td>• Risk of infection (screen for TB and Viral hepatitis)</td>
</tr>
<tr>
<td></td>
<td>• Risk of Heart Failure and pericarditis</td>
</tr>
<tr>
<td></td>
<td>• Hepatosplenic T-cell lymphoma when used with azathioprine or 6-MP in young male patients</td>
</tr>
<tr>
<td></td>
<td>• Antibody formation</td>
</tr>
<tr>
<td>Antimotility agents</td>
<td>• Risk of toxic megacolon in active disease</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>• Bone marrow suppression, pancreatitis, hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>• Need to check TPMT activity</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>• Bone marrow suppression, pulmonary and hepatic toxicity</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>• Adrenal suppression, metabolic effects, infection</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>• Progressive multifocal leukoencephalopathy</td>
</tr>
</tbody>
</table>

Patient Case #4
- What would be an appropriate modification of his drug regimen at this time?
  - Change balsalazide to sulfasalazine 6g/day
  - Initiate therapy with methotrexate IM weekly
  - Initiate infliximab and taper prednisone
  - Add mesalamine suppository daily

Handout Page 1-100; Answer Page 1-137

Patient Case #5
- HPI: 25 year old woman with Crohn’s disease. Presents with a 2 day history of crampy abdominal pain, fever, fatigue, and 10-12 bloody stools per day.
- MEDS: Pentasa 250mg #4 caps 2 times/day
- PMH: Crohn’s Disease x 5 years
- Vitals: Temp 101F, HR=110, RR=18, BP = 118/68

Handout Page 1-100; Answer Page 1-138

Patient Case #6
- HPI: 47 year old woman with nausea, abdominal pain, fever. Abdominal distention with tenderness and shifting dullness.
- PMH: Cirrhosis (Class C)
- MEDS: Furosemide, spironolactone
- Diagnostics: Paracentesis (albumin 0.9 g/dl, WBC 1000/mm³)

Handout Page 1-107; Answer Page 1-138

Patient Case #6
- Which recommendation is best at this time for treatment of this patient’s hepatic encephalopathy?
  - A. Intravenous albumin
  - B. Intravenous vancomycin plus tobramycin
  - C. Intravenous cefotaxime plus albumin
  - D. Oral trimethoprim/sulfamethoxazole DS daily

Handout Page 1-107; Answer Page 1-138
Complications of Cirrhosis

- Variceal bleeding
- Ascites
- Infection
- Mortality
- Hepatorenal Syndrome
- Hepatopulmonary Syndrome
- Encephalopathy

Spontaneous Bacterial Peritonitis
- Definition: Primary infection of the ascitic fluid
- Pathogens
  - Enteric gram negatives
  - Streptococci
- Clinical features
  - Fever, abdominal pain, AMS, vomiting
  - High risk of hepatorenal syndrome, increased mortality
  - Ascitic fluid PMN > 250 mm$^3$

SBP Treatment and Prevention
- Treatment: 3rd gen Cephalosporin + albumin
- Primary Prevention
  - During setting of an acute GI bleed
  - Ascitic fluid protein < 1.5 g/dl + Scr > 1.2 mg/dl or BUN > 25 mg/dl or Na < 130 mEq/L, or CP > 9 with bilirubin > 3 mg/dl
- Secondary Prevention: any patient with prior episode
  - Hospital: Ceftriaxone/Cefotaxime, Fluoroquinolone
  - Outpatient: TMP/SMX, Norfloxacin/ciprofloxacin

Patient Case #6
- Which recommendation is best at this time for treatment of this patient’s SBP?
  - Intravenous albumin
  - Intravenous vancomycin plus tobramycin
  - Intravenous cefotaxime plus albumin
  - Oral trimethoprim/sulfamethoxazole DS daily

Patient Case #7
- HPI: 36 year old female with 36 hours of hematemesis, fatigue, dizziness, black tarry stools.
- PMH: Cirrhosis, alcohol abuse, MI (2 years ago)
- Diagnostics: EGD several large esophageal varices that are banded.

Patient Case #7
- In addition to the endoscopic band ligation which of the pharmacologic interventions is best?
  - A. Nadolol 20mg orally once a day x 3 days
  - B. Vasopressin continuous infusion x 2 days
  - C. Octreotide 50 ug bolus, then 50 ug/hr for 5 days
  - D. Pantoprazole 80mg bolus, then 8mg/hr x 72 hours
Variceal Bleeding

- Varices: Collateral vessels formed secondary to increased resistance to blood flow within the liver
- Bleeding risk
  - 25-35% of patient with cirrhosis
  - 30-50% mortality per bleed
- High recurrence rate
  - ~70% within first month of bleed

Treatment of Variceal Bleeding

- Stabilization + IV fluids
- Endoscopic interventions
  - Sclerotherapy
  - Band ligation
- Medical Management
  - Vasopressin + nitroglycerin
  - Octreotide x 3-5 days
  - Antibiotics (3rd Gen Ceph or Fluoroquinolone)

Prevention of Variceal Bleeding

- Pharmacologic +/- endoscopic
  - Primary prevention
    - Small varices + high bleeding risk
    - Medium/Large varices
    - Non selective beta blockers
  - Secondary prevention
    - All patients with history of bleeding
    - Non selective beta blockers
    - Endoscopic (band ligation)

Patient Case #7

- In addition to the endoscopic band ligation which of the pharmacologic interventions is best?
  - Nadolol 20mg orally once a day x 3 days
  - Vasopressin continuous infusion x 2 days
  - Octreotide 50 ug bolus, then 50 ug/hr for 5 days
  - Pantoprazole 80mg bolus, then 8mg/hr x 72 hours

Patient Case #8

- HPI: 45-year old woman with history of IVDA. Diagnosed 8 months ago with HBV. Treatment naive. No ascites or encephalopathy.
  - Diagnostics:
    - AST 650 IU/ml, ALT 850 IU/ml
    - HBSAg (+), HBeAg (+), YMDD mutation
    - HBV DNA 107, 000 IU/ml
    - Biopsy: severe necroinflammation/bridging fibrosis

- What is the most appropriate course of action at this time?
  - A. No treatment; Recheck HBV DNA in 6 months
  - B. Initiate PEG-IFN + ribavirin
  - C. Initiate lamivudine 100 mg/day
  - D. Initiate tenofovir 300 mg/day
Hepatitis B

- DNA Virus, Genotypes A-H
- Transmission
  - Parenteral, bodily fluids, sexual contact, perinatal
- Detect via serologies, symptoms, LFTs
  - Patients with active disease will be HBsAg (+)
- Treat patients with chronic disease (> 6 months)
  - > 2 x ALT, HBV DNA > 20,000 IU/ml

Chronic Hepatitis B Treatment

- Need to distinguish if HBV:
  - is HBeAg positive or negative
  - Harbors the “YMDD mutation” of the DNA polymerase
- Difficult patient populations
  - Decompensated liver disease
  - Co-infection
  - Treatment experienced

Summary of HBV Treatment Recommendations

<table>
<thead>
<tr>
<th>HBV Population</th>
<th>Preferred Treatment Options</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>Entecavir and tenofovir are preferred oral agents</td>
<td>Minimum of 1 year</td>
<td>Preferred if contraindications or nonresponse to INFs</td>
</tr>
<tr>
<td></td>
<td>Use of other oral reverse transcriptase inhibitors is possible but not preferred</td>
<td>INFs 48 weeks</td>
<td>If contraindication or no response, use entecavir and tenofovir</td>
</tr>
<tr>
<td></td>
<td>PEG-INFs 120 weeks</td>
<td>INFs 48 weeks</td>
<td>If contraindication or no response, use entecavir and tenofovir</td>
</tr>
</tbody>
</table>

Hepatitis 2009;50(3):1-36

Hepatitis B Treatment

Nucleoside Analog Adverse Effects

- Class effects
  - Rebound hepatitis upon discontinuation
  - GI Effects (N/V/D/Abdominal pain)
  - HIV resistance
  - Lactic Acidosis (rare)
  - Reductions in bone mineral density
- Nephrotoxicity (adefovir)
- Telbivudine
  - Elevations in CK
  - Elevation in CK
  - Peripheral neuropathy
- Renally dose all medications

Patient Case #8

- What is the most appropriate course of action at this time?
  - No treatment; Recheck HBV DNA in 6 months
  - Initiate PEG-INF + ribavirin
  - Initiate lamivudine 100 mg/day
  - Initiate tenofovir 300 mg/day

Patient Case #9

- HPI: 38 year old male with chronic hepatitis C (genotype 1) currently undergoing treatment
- Evaluated at 12 week follow up appointment after starting treatment.
- MEDS: Pegylated interferon + ribavirin
- LABS:
  - AST 90 IU/ml (350 IU/ml), ALT 64 IU/ml (420 IU/ml)
  - HCV RNA 3500 IU/ml (450,000 IU/ml)
Patient Case #9

What is the most appropriate course of action at this time?

A. Discontinue therapy and monitor for symptoms
B. Continue treatment for an additional 12 weeks
C. Add boceprevir for an additional 12 weeks
D. Continue treatment for an additional 72 weeks

Hepatitis C

RNA Virus
- Genotypes 1-6 (1-3 most common is US)
  - Several subtypes
  - Genotype 1 most resistant to drug treatment
  - Transfusion, IV drug abuse, transplant

- Major cause of chronic liver disease
  - 60-80% progression following acute infection
  - #1 reason for transplant

Hepatitis C RNA Virus
- Genotypes 1-6 (1-3 most common is US)
  - Several subtypes
  - Genotype 1 most resistant to drug treatment
  - Transfusion, IV drug abuse, transplant

- Major cause of chronic liver disease
  - 60-80% progression following acute infection
  - #1 reason for transplant

Treatment of Chronic Hepatitis C

- First line:
  - Genotype 1: Pegylated interferon + ribavirin + telaprevir OR boceprevir
  - Genotypes 2 and 3: Pegylated interferon + ribavirin

- Pegylated Interferon Dosing:
  - Pegasys: 180 μg SQ Weekly
  - Peg Intron: 1-1.5 μg/kg/week SQ

- Ribavirin orally in 2 divided doses:
  - Dose differs based on genotype, weight, and interferon product

Direct Acting Antivirals (DAAs)

Telaprevir (Incivek®)

- FDA Approved indication
  - Chronic HCV genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (≥ 18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

- Dose
  - 750 mg three times daily for 12 weeks followed by PEG-INF and ribavirin x 12 weeks if undetectable HCV RNA at week 4 and 12.
  - 375 mg tablets
  - Give doses 7-9 hours apart; give with meal that has at least 20 g fat ingested 20 minutes prior
  - Take missed doses if within 4 hours

- 800 mg orally three times daily starting after 4 weeks of PEG-INF and ribavirin
  - 200 mg capsules
  - Give doses 7-9 hours apart; give with meal or light snack
  - Take missed doses if within 2 hours

Boceprevir (Victrelis®)

- FDA Approved indication
  - Chronic HCV genotype 1 infection, in combination with peginterferon alfa and ribavirin in patients with compensated liver disease

- Dose
  - 800 mg orally three times daily starting after 4 weeks of PEG-INF and ribavirin
  - 200 mg capsules
  - Give doses 7-9 hours apart; give with meal or light snack
  - Take missed doses if within 2 hours

DAA Safety

- Both contraindicated in pregnancy and in male partners of pregnant women

- Telaprevir
  - Rash (up to 56%) maculopapular/eczematous
  - DRESS, Stevens Johnson Syndrome
  - Anemia, pruritus, nausea

- Boceprevir
  - Anemia, neutropenia, fatigue, dysgeusia
**DAA Drug Interactions**

- Both are potent CYP 3A4/5 inhibitors
- Several CYP3A4 substrates or inducers are contraindicated

<table>
<thead>
<tr>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>Cisapride</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Tadalafil, sildenafil</td>
<td>Drosperinone</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Atorvastatin, lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral triazolam or midazolam</td>
<td>Carbamazepine, phenytoin, phenobarbital</td>
</tr>
</tbody>
</table>

**May narrow therapeutic index drugs must be adjusted**
- Antiarrhythmics (amiodarone, flecainide, propafenone)
- Digoxin
- Warfarin
- Bosentan
- Azole antifungals
- Coldicine
- Clarithromycin
- Rifabutin
- DHP calcium channel blockers
- Dexamethasone
- Inhaled budesonide and fluticasone
- Methadone
- Cyclosporine/tacrolimus

**HCV Monitoring**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Virological Response (RVR)</td>
<td>Negative HCV RNA at week 4 of treatment</td>
</tr>
<tr>
<td>Early Virological Response (EVR)</td>
<td>&gt; 2 log decline in HCV RNA compared to baseline or negative HCV RNA at 12 weeks</td>
</tr>
<tr>
<td>End of Treatment Response (ETR)</td>
<td>Negative HCV RNA at the end of a 24 or 48 week course depending on genotype</td>
</tr>
<tr>
<td>Sustained Virological Response (SVR)</td>
<td>Negative HCV RNA 24 weeks after finishing treatment</td>
</tr>
</tbody>
</table>

**Chronic Hepatitis C Treatment Duration**

- **Genotype 1:**
  - It depends…..
- **Genotypes 2 and 3:** 24 weeks

<table>
<thead>
<tr>
<th>Region</th>
<th>Patient Group</th>
<th>HCV RNA Week 4</th>
<th>HCV RNA Week 8</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-INF + Ribavirin + Telaprevir</td>
<td></td>
<td></td>
<td></td>
<td>Treatment naive or prior relapse</td>
</tr>
<tr>
<td>Previously naïve or prior relapse</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 drugs for 24 weeks total</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Then continue Peg-INF and ribavirin for through week 48</td>
<td></td>
</tr>
<tr>
<td>Prior partial response or relapse</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 drugs for 36 weeks total</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Then continue Peg-INF and ribavirin for through week 48</td>
<td></td>
</tr>
<tr>
<td>Patients with HCV RNA &gt; 100 IU/ml at week 24</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Discontinue all 3 drugs</td>
<td></td>
</tr>
<tr>
<td>Patients with HCV RNA &gt; 100 IU/ml at week 12 or detectable HCV RNA at week 24</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 drugs for 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Chronic Hepatitis C Treatment Duration**

<table>
<thead>
<tr>
<th>Region</th>
<th>Patient Group</th>
<th>HCV RNA Week 4</th>
<th>HCV RNA Week 12</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-INF + Ribavirin + Telaprevir</td>
<td></td>
<td></td>
<td></td>
<td>Treatment naive or prior relapse</td>
</tr>
<tr>
<td>Treatment naïve or prior relapse</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>1. Continue all 3 drugs for 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Then treat with Peg-INF and ribavirin for an additional 12 weeks (24 weeks total)</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>&lt;1000 IU/ml</td>
<td>&lt;1000 IU/ml</td>
<td>1. Discontinue all 3 drugs at week 12</td>
<td></td>
</tr>
</tbody>
</table>

Detectable HCV RNA at 24 weeks | Undetectable | Undetectable | 1. Discontinue Peg-INF and ribavirin
Patient Case #9

- What is the most appropriate course of action at this time?
  - Discontinue therapy and monitor for symptoms
  - Continue treatment for an additional 12 weeks
  - Add boceprevir for an additional 12 weeks
  - Continue treatment for an additional 72 weeks

Handout Page 1-121; Answer Page 1-138

Patient Case #10

- HPI: 55 year old man with chronic alcohol abuse and chronic pancreatitis. Steatorrhea and weight loss (now 135 lb)
- LABS: Albumin 2.1 g/dl, Fecal fat 20g/day
- Medications: morphine CR, oxycodone IR as needed

Handout Page 1-134; Answer Page 1-139

Patient Case #10

- What is the best course of action for this patient?
  - A. Increase morphine CR to 60 mg twice daily
  - B. Initiate dronabinol to improve appetite
  - C. Initiate pancrelipase 30,000 units/meal
  - D. Add a multivitamin to his regimen

Handout Page 1-134; Answer Page 1-139

Overview

Pancreatitis

Acute
- Mild-Severe Inflammation
- Generally reversible exocrine and/or endocrine function
- Rarely progresses to chronic
- Pain, N/V, sepsis, organ dysfunction

Chronic
- Longstanding pancreatic injury
- Fibrosis/destruction of tissue
- Irreversible exocrine and/or endocrine function
- Pain, steatorrhea, malnutrition, diabetes

Acute Pancreatitis
- Largely supportive Care
- Pain management
- Antiemetics
- Nutritional support
  - Enteral
  - Hyperglycemia
- Antibiotics
  - Infection, abscess, or necrosis

Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Targeted Therapies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Narcotic +/- non-narcotic therapies</td>
<td>Acetaminophen and/or NSAIDs + Long acting narcotic preparations + IR breakthrough + Caution with acetaminophen and narcotics if alcohol use is continued</td>
</tr>
<tr>
<td></td>
<td>Pancreatic enzymes</td>
<td></td>
</tr>
<tr>
<td>Malabsorption and Malnutrition</td>
<td>Pancreatic enzymes</td>
<td>Start around 30,000-40,000 lipase units per meal; ½ dose for snacks + Do not crash or chew + Max 2500 u/kg/dose; 10,000 u/kg/day + Titrated to steatorrhea + weight gain + Porcine based so avoid if pork allergy + ADEK</td>
</tr>
<tr>
<td></td>
<td>Fat soluble vitamins</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Insulin</td>
<td>Long acting + short acting + Oral intake may be variable</td>
</tr>
</tbody>
</table>
Patient Case #10

What is the best course of action for this patient?

- Increase morphine CR to 60 mg twice daily
- Initiate dronabinol to improve appetite
- Initiate pancrelipase 30,000 units/meal
- Add a multivitamin to his regimen

Handout Page 1-134; Answer Page 1-139

Patient Case #11

HPI: 32 year old woman with crampy abdominal pain, bloating and constipation for 6 months. Not food related. Diagnosed with IBS-C.

- LABS: within normal limits
- Medications and allergies: none

Handout Page 1-134; Answer Page 1-139

Patient Case #11

A. Which of the following therapeutic interventions is best for this patient?

B. Amitriptyline 50 mg/day
C. Senna 2 tablets twice daily
D. Tegaserod 6 mg twice daily
D. Lubiprostone 8 mcg twice daily

Handout Page 1-134; Answer Page 1-139

Irritable bowel syndrome

- Categories
  - Diarrhea Predominant (IBS-D)
  - Constipation Predominant (IBS-C)
  - Mixed Pattern (IBS-M)
- Features
  - Change in frequency and/or stool appearance
  - Pain, bloating, Relief with defecation
- Target main symptoms and comorbidities

Therapies | Comments
---|---
Hyoscine, dicyclomine | Target pain due to spasm and also treat diarrhea
Tricyclic antidepressants | Target pain and diarrhea
  - Generally reserved for IBS-D
  - Low doses
SSRIs, SNRIs | Target pain and often have promotility action in IBS-D
  - Can also treat comorbid depression and anxiety
Lubiprostone | Indicated for IBS-C in women > 18 years
  - Main adverse effect is nausea, more expensive option
Loperamide | Adjunctive for IBS-D, but does not treat pain
Probiotics | Some potential improvement in global symptoms and pain
Alosetron | Indicated for IBS-D in women > 18 years failing other therapies
  - Must be enrolled in prescribing program
  - Risk of ischemic colitis
Tegaserod | Indication: IBS-C, available on emergency use only due to CV risk
Rifaximin | Some data to support improvement in bloating

Patient Case #11

- Which of the following therapeutic interventions is best for this patient?

  B. Amitriptyline 50 mg/day
  C. Senna 2 tablets twice daily
  D. Tegaserod 6 mg twice daily
  D. Lubiprostone 8 mcg twice daily

Handout Page 1-134; Answer Page 1-139
Patient Case #12

- HPI: 30 year old pregnant woman (14 weeks) with myalgias, watery diarrhea (4-5), vomiting x 1.
- Labs: influenza (-), WBC 8000 x 10^3
- Medications: prenatal vitamin
- Allergies: none

Management of Diarrhea

- Remove correct underlying cause
  - Identify drug-induced causes
- Rehydration
  - ORS
  - Parenteral
- Dietary modification

Antidiarrheal Preparations

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>• OTC and prescription products, tablet and liquid&lt;br&gt;• OTC indicated in age &gt; 6&lt;br&gt;• Pregnancy category B</td>
</tr>
<tr>
<td>Opioids (diphenoxylate, tincture of opium)</td>
<td>• Generally reserved for more severe cases&lt;br&gt;• Increased risk of CNS adverse effects</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>• OTC tablet and liquid preparations&lt;br&gt;• Avoid:&lt;br&gt;  - Patients &lt; 12 years of age&lt;br&gt;  - Pregnancy&lt;br&gt;  - Salicylate allergy&lt;br&gt;  - Signs/symptoms of bleeding or mucous&lt;br&gt;  - Stool and tongue discoloration&lt;br&gt;  - Chelation interactions</td>
</tr>
<tr>
<td>Lactase</td>
<td>• Suspected or diagnosed lactose intolerance</td>
</tr>
<tr>
<td>Probiotics</td>
<td>• Data in AAD, IBD, IBS, radiation induced</td>
</tr>
</tbody>
</table>

Patient Case #12

- What is the most appropriate course of action at this time for this patient's diarrhea?
  - A. Loperamide
  - B. Bismuth subsalicylate
  - C. Lactase
  - D. Pyridoxine

THE END